IgA nephropathy update

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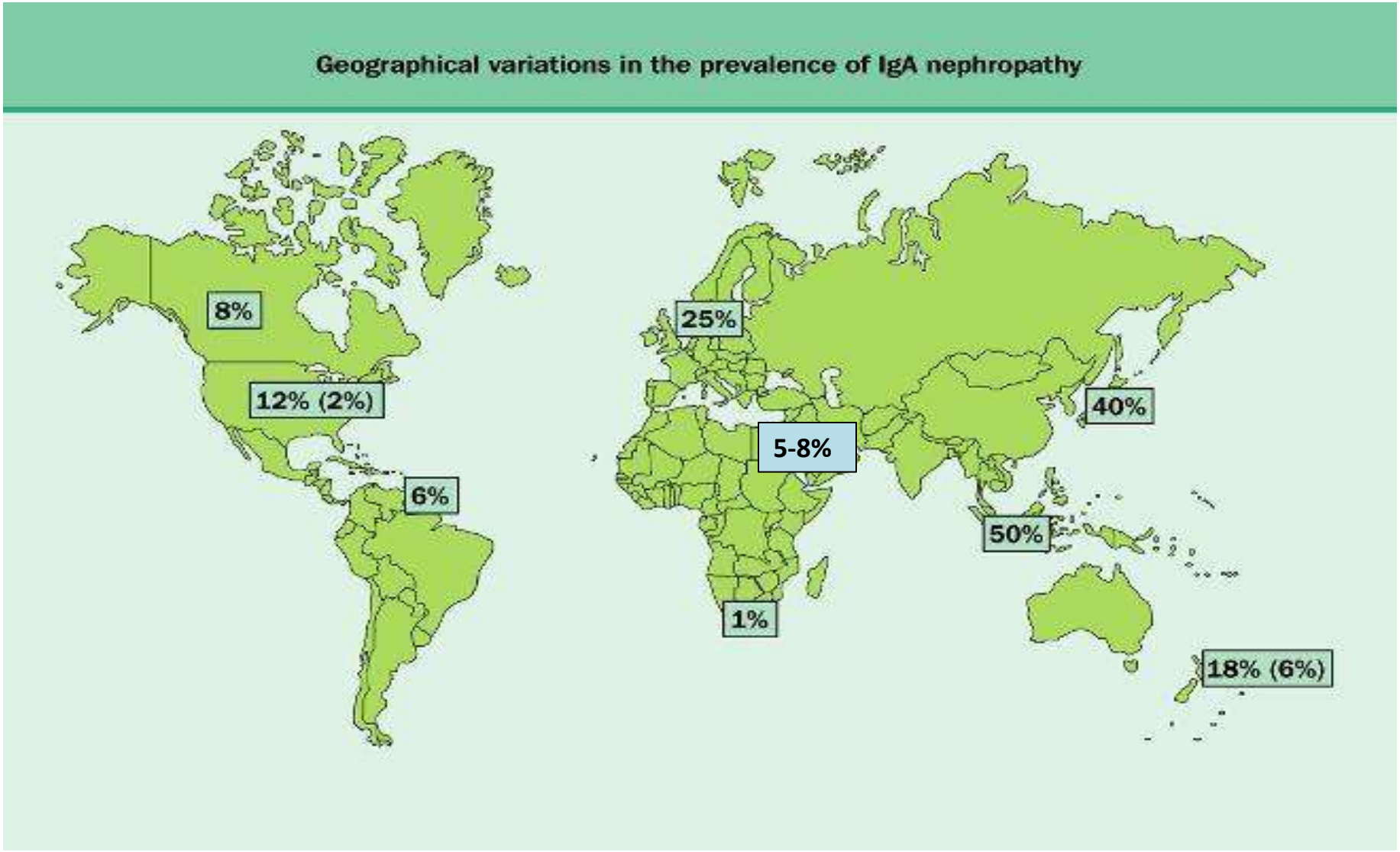
IgA nephropathy

- IgAN is defined as **dominant or codominant staining with IgA** in glomeruli by immuno-histology thus, IgAN is diagnosed by kidney biopsy.
- IgAN is the **most common primary GN** in the world (30-35%). The prevalence rate varies across different geographical regions.

IgA nephropathy

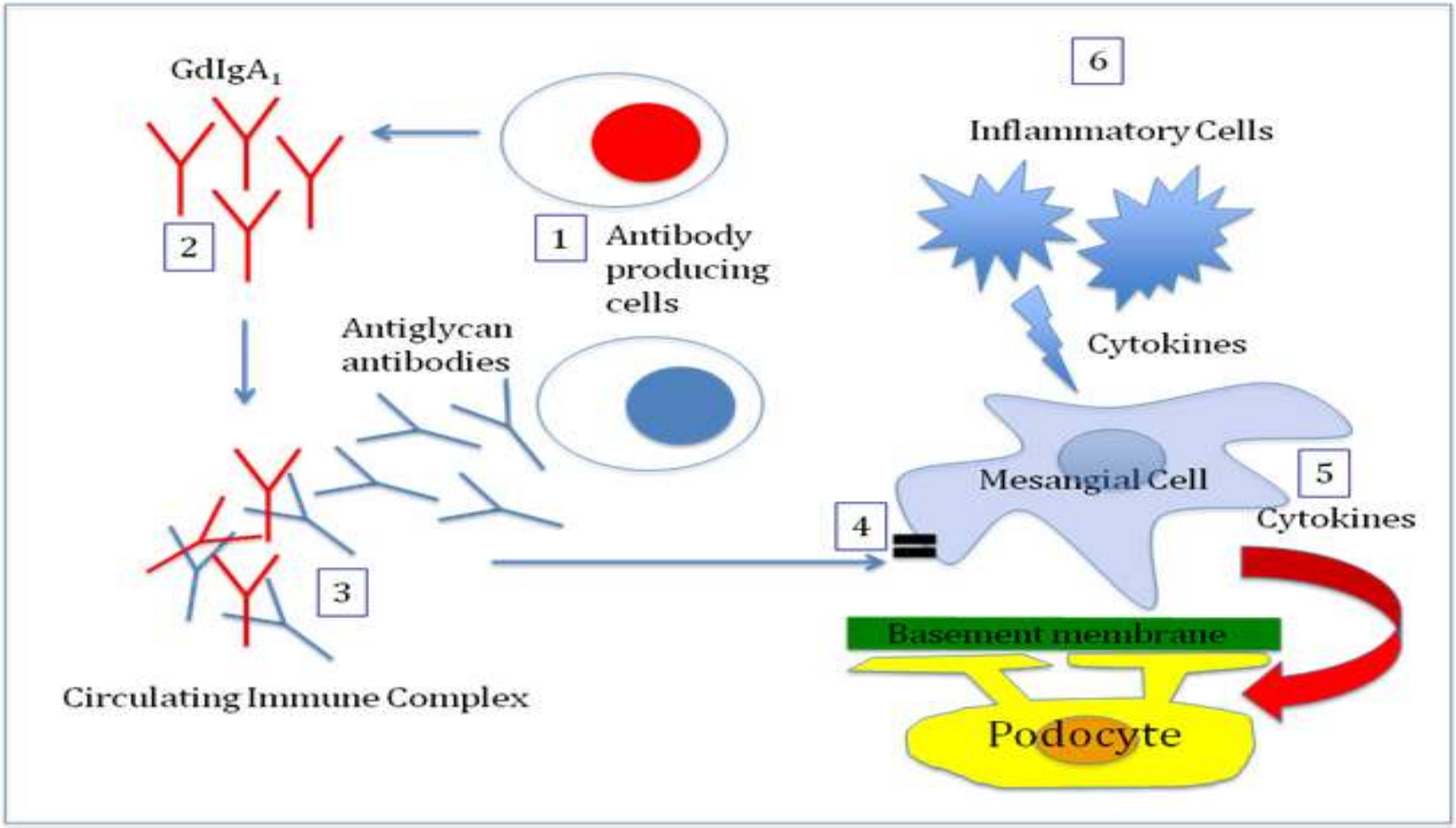


IgA nephropathy

Secondary IgAN is is uncommon and may be caused by:

- Cirrhosis
- Celiac disease
- HIV infection
- Dermatitis herpetiformis
- Seronegative arthritis (particularly ankylosing spondylitis)
- Small-cell carcinoma
- Lymphoma
- Disseminated tuberculosis, bronchiolitis obliterans
- Inflammatory bowel disease (Crohn’s disease and ulcerative colitis).

IgA nephropathy pathogenesis



Clinical presentation of IgAN

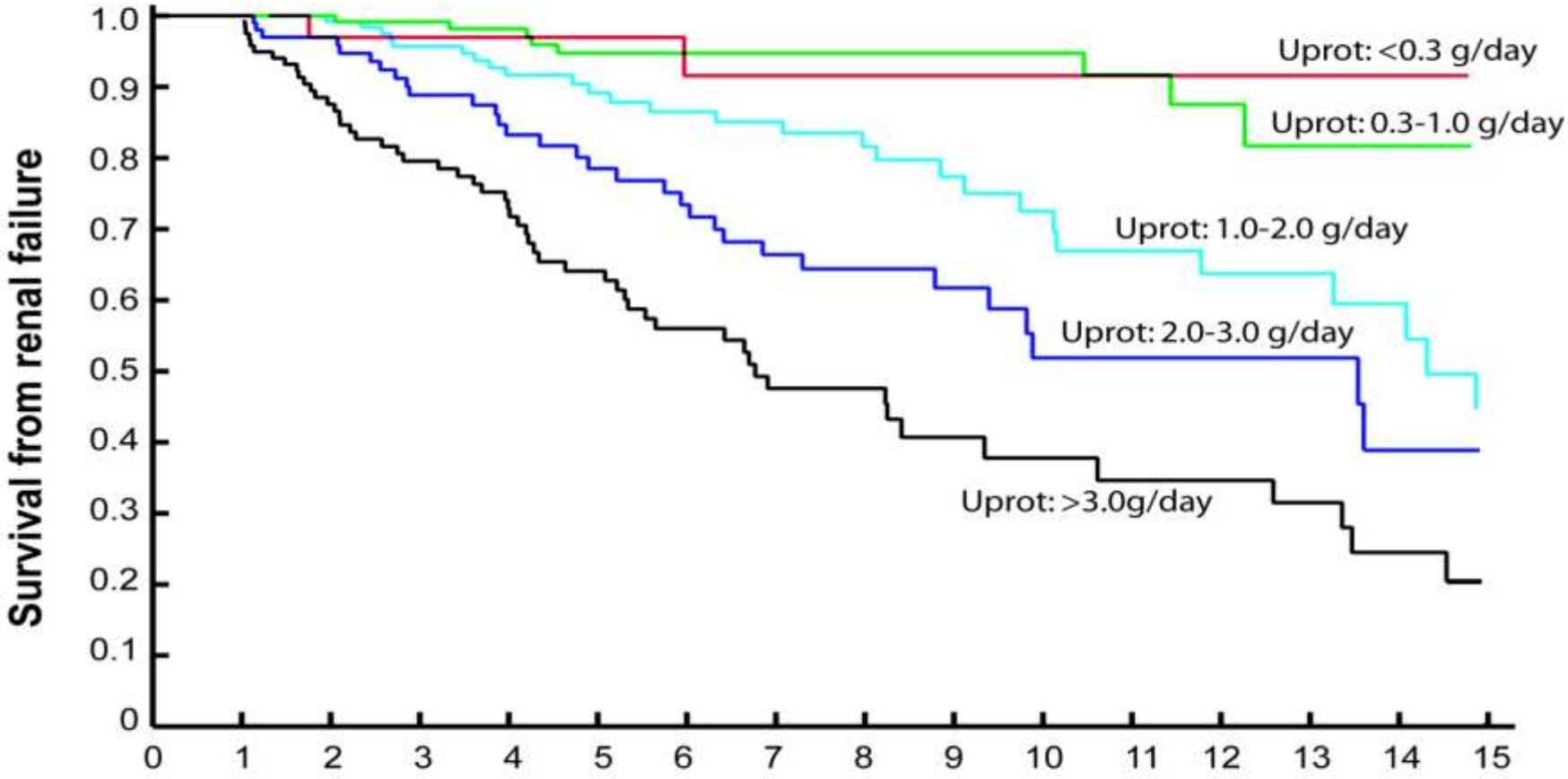
1. Asymptomatic microscopic hematuria with episodes of macroscopic hematuria, mild proteinuria (80%).
2. Acute nephritic syndrome(10%).
3. Atypical presentations:

- Nephrotic syndrome.
- RPGN cresentic GN.
- AKI with macroscopic hematuria.
- CKD.

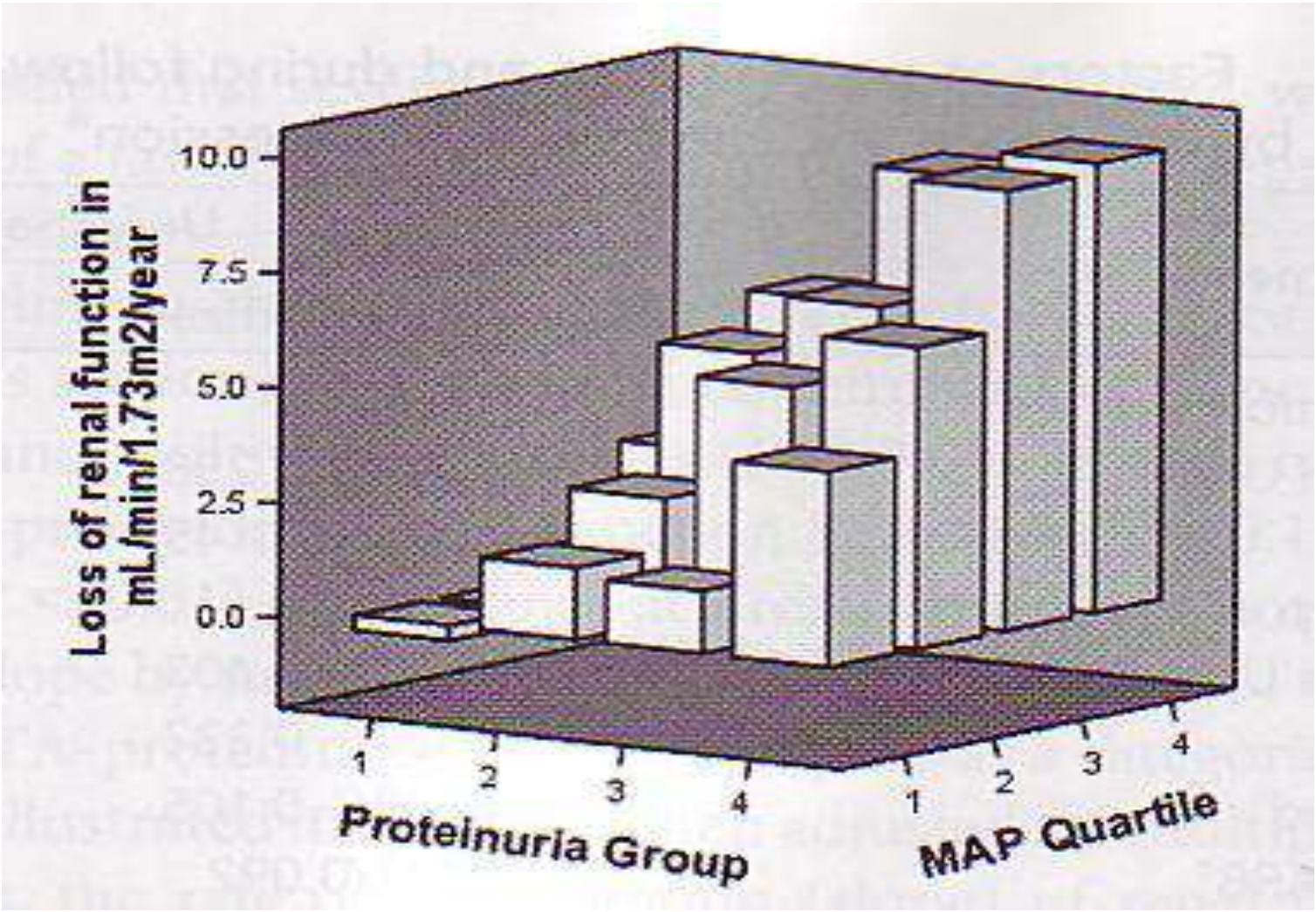
Risk of progression of IgAN

- Thorough risk assessment is essential to determine management option proportionate to the risk of progression.

Renal survival and average follow-up proteinuria in IgA patients from the GN registry



Uprot				
<0.3	36	24	9	3
0.3-1	135	93	50	19
1-2	136	86	40	18
2-3	103	58	24	12
>3	121	63	22	11



Reich H et al. JASN 2007; 18: 3177

MEST score

The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society:

Mesangial hypercellularity - in > or <50% of glomeruli	**M0 or M1**
Endocapillary hypercellularity – present/absent	**E0 or E1**
Segmental sclerosis/adhesions – present/absent	**S0 or S1**
Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, >50%	**T0 or T1 or T2**

PREDICTING PROGRESSION IN IgA NEPHROPATHY

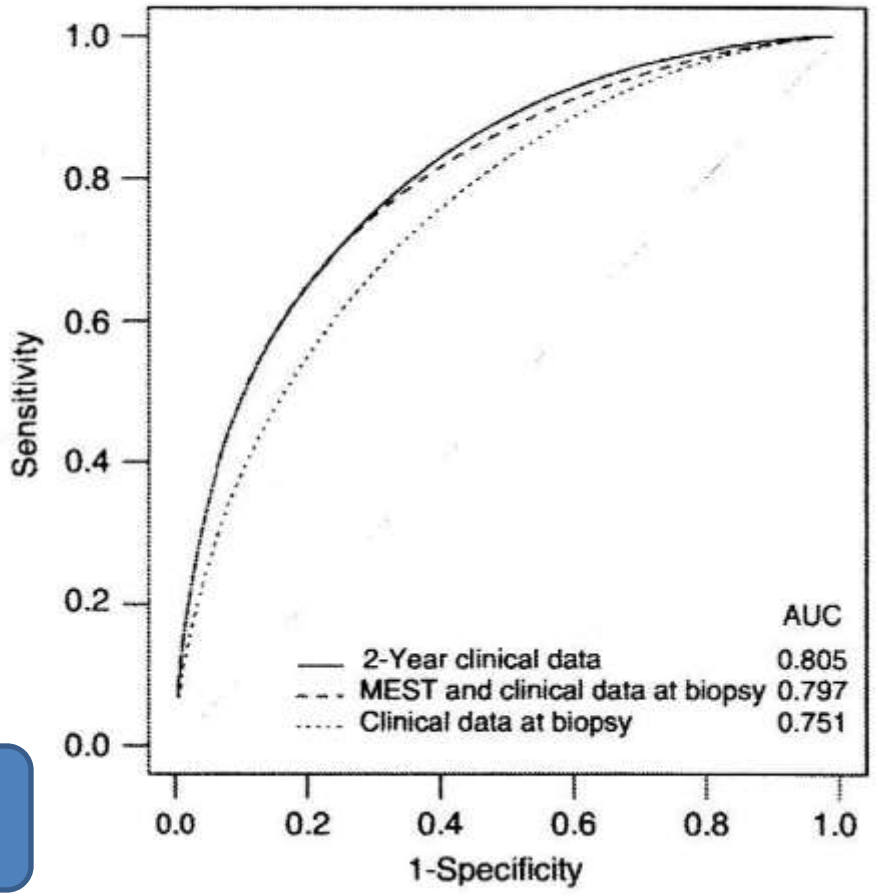
Clinical data at time of biopsy
Proteinuria
Blood pressure

+

Pathological data
MEST score

=

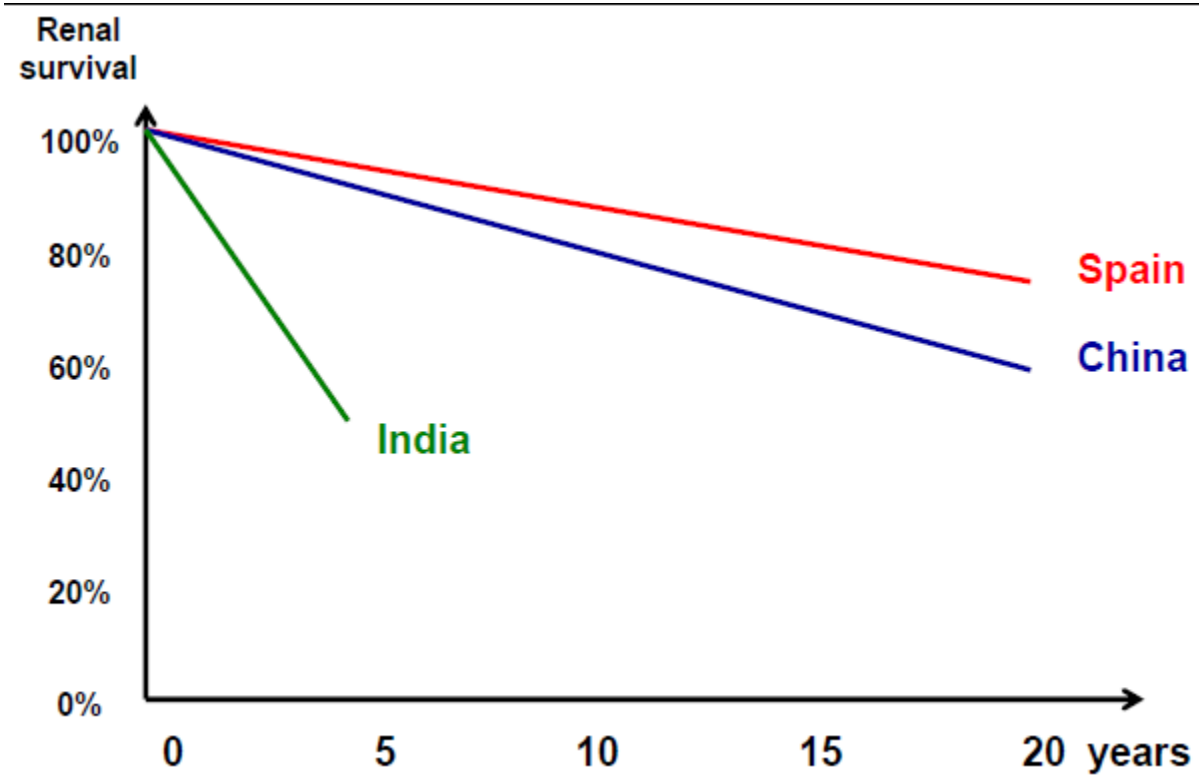
Outcome prediction as good as clinical data after 2 years follow up



Barbour S *et al.* KI 2015, e-pub

Other progression risk factors for IgAN

- Initial GFR at presentation (no evidence).
- Obesity (confounder with proteinuria).
- Adulthood presentation(lower GFR, higher BP than childhood type).
- Geographical or ethnic variations in outcomes


Renal survival
100%
80%
60%
40%
20%
0%
0
5
10
15
20 years
Spain
China
India

Management of IgA Nephropathy

- **Role of non-immunosuppressive medications**
- **Role of immunosuppressive medications**

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

kidney INTERNATIONAL supplements

KI Supplements 2012
2(2): 1-274

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES ®

KDIGO

CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS

Evidence-based consensus treatment guidelines Including treatment of IgA nephropathy & HSP nephritis

Co-chairs:
Dan Cattran (Canada)
John Feehally (UK)

Role of non- immunosuppressive medications

Management of slowly progressive IgA nephropathy

Target Blood Pressure

Proteinuria < 1g/24hr 130/80

Proteinuria > 1g/24hr 125/75

RAS Blockade

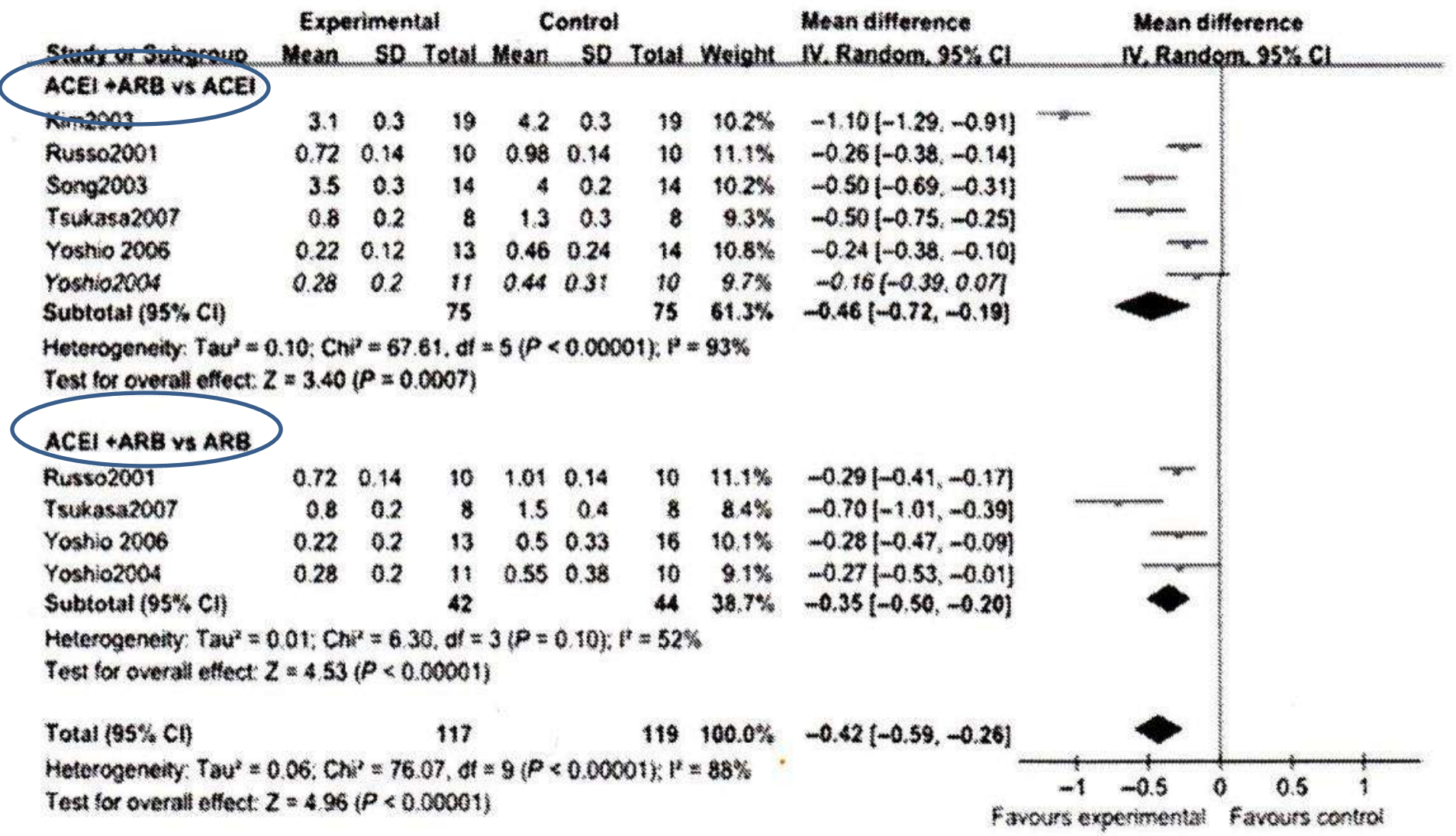
Proteinuria > 1g/24hr 125/75

Combination therapy ?

Non-immunosuppressive treatment for IgA nephropathy (Review)

Reid S, Cawthon PM, Craig JC, Samuels JA, Molony DA, Strippoli GFM

THE COCHRANE COLLABORATION®


Experimental
Control
Mean difference
Mean difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
ACEI +ARB vs ACEI
Kim2003 3.1 0.3 19 4.2 0.3 19 10.2% −1.10 [−1.29, −0.91]
Russo2001 0.72 0.14 10 0.98 0.14 10 11.1% −0.26 [−0.38, −0.14]
Song2003 3.5 0.3 14 4 0.2 14 10.2% −0.50 [−0.69, −0.31]
Tsukasa2007 0.8 0.2 8 1.3 0.3 8 9.3% −0.50 [−0.75, −0.25]
Yoshio 2006 0.22 0.12 13 0.46 0.24 14 10.8% −0.24 [−0.38, −0.10]
Yoshio2004 0.28 0.2 11 0.44 0.31 10 9.7% −0.16 [−0.39, 0.07]
Subtotal (95% CI) 75 75 61.3% −0.46 [−0.72, −0.19]
Heterogeneity: Tau² = 0.10; Chi² = 67.61, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.40 (P = 0.0007)
ACEI +ARB vs ARB
Russo2001 0.72 0.14 10 1.01 0.14 10 11.1% −0.29 [−0.41, −0.17]
Tsukasa2007 0.8 0.2 8 1.5 0.4 8 8.4% −0.70 [−1.01, −0.39]
Yoshio 2006 0.22 0.2 13 0.5 0.33 16 10.1% −0.28 [−0.47, −0.09]
Yoshio2004 0.28 0.2 11 0.55 0.38 10 9.1% −0.27 [−0.53, −0.01]
Subtotal (95% CI) 42 44 38.7% −0.35 [−0.50, −0.20]
Heterogeneity: Tau² = 0.01; Chi² = 6.30, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 4.53 (P < 0.00001)
Total (95% CI) 117 119 100.0% −0.42 [−0.59, −0.26]
Heterogeneity: Tau² = 0.06; Chi² = 76.07, df = 9 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.96 (P < 0.00001)
−1
−0.5
0
0.5
1
Favours experimental
Favours control

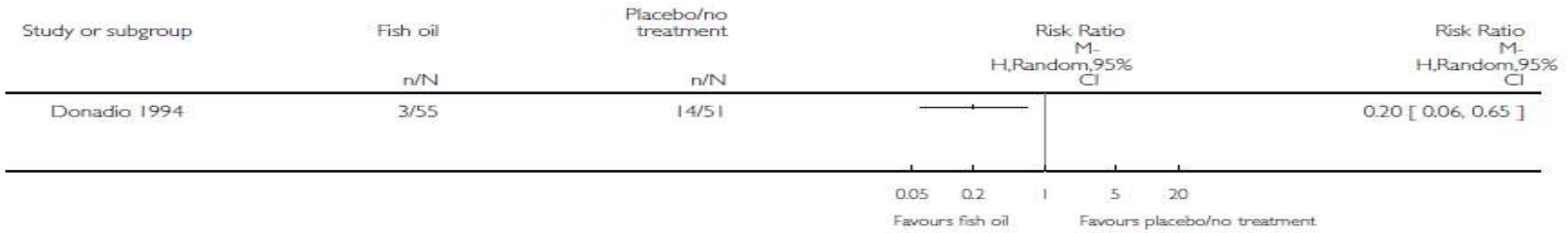
Fish oil

Analysis 1.2. Comparison 1 Fish oil versus placebo/no treatment, Outcome 2 > 50% increase in serum creatinine.

Review: Non-immunosuppressive treatment for IgA nephropathy

Comparison: 1 Fish oil versus placebo/no treatment

Outcome: 2 > 50% increase in serum creatinine

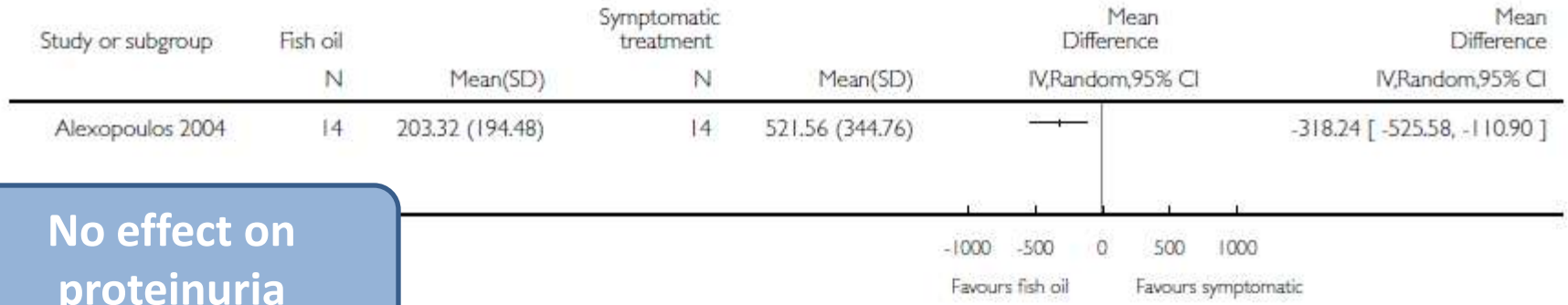


Analysis 2.4. Comparison 2 Fish oil versus symptomatic treatment, Outcome 4 Serum creatinine.

Review: Non-immunosuppressive treatment for IgA nephropathy

Comparison: 2 Fish oil versus symptomatic treatment

Outcome: 4 Serum creatinine



No effect on proteinuria

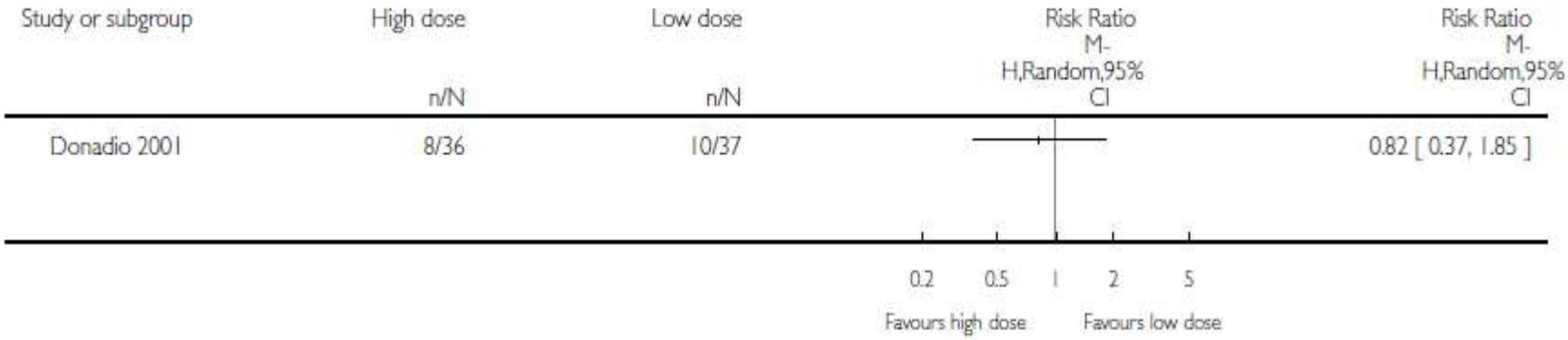
Fish oil (high dose vs low dose)

Analysis 3.1. Comparison 3 Fish oil: high versus low dose, Outcome 1 ESKD.

Review: Non-immunosuppressive treatment for IgA nephropathy

Comparison: 3 Fish oil: high versus low dose

Outcome: 1 ESKD



No significant effect of dose

Fish oil and Omega 3 polyunsaturated fatty acids

- Omega 3 polyunsaturated fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major n-3 fatty acids that serve as substrates for cyclooxygenase and lipoxygenase pathways leading to **less potent inflammatory mediators**.
- In addition, potential targets of n-3 PUFA relevant to renal disease progression could be through **lowering blood pressure**, reducing serum lipid levels, decreasing vascular resistance, or preventing thrombosis.

Fish oil and Omega 3 polyunsaturated fatty acids

- Treatment for 2 years with a daily dose of 1.8 g of EPA and 1.2 g of DHA slowed the progression of renal disease in high-risk patients with no significant reduction of proteinuria.

Donadio et al, Semin Nephrol 2004;24(3):225-43.

Antiplatelet and anticoagulants

Analysis 10.5. Comparison 10 Anticoagulant+other treatment versus other treatment, Outcome 5 Proteinuria.

Review: Non-immunosuppressive treatment for IgA nephropathy

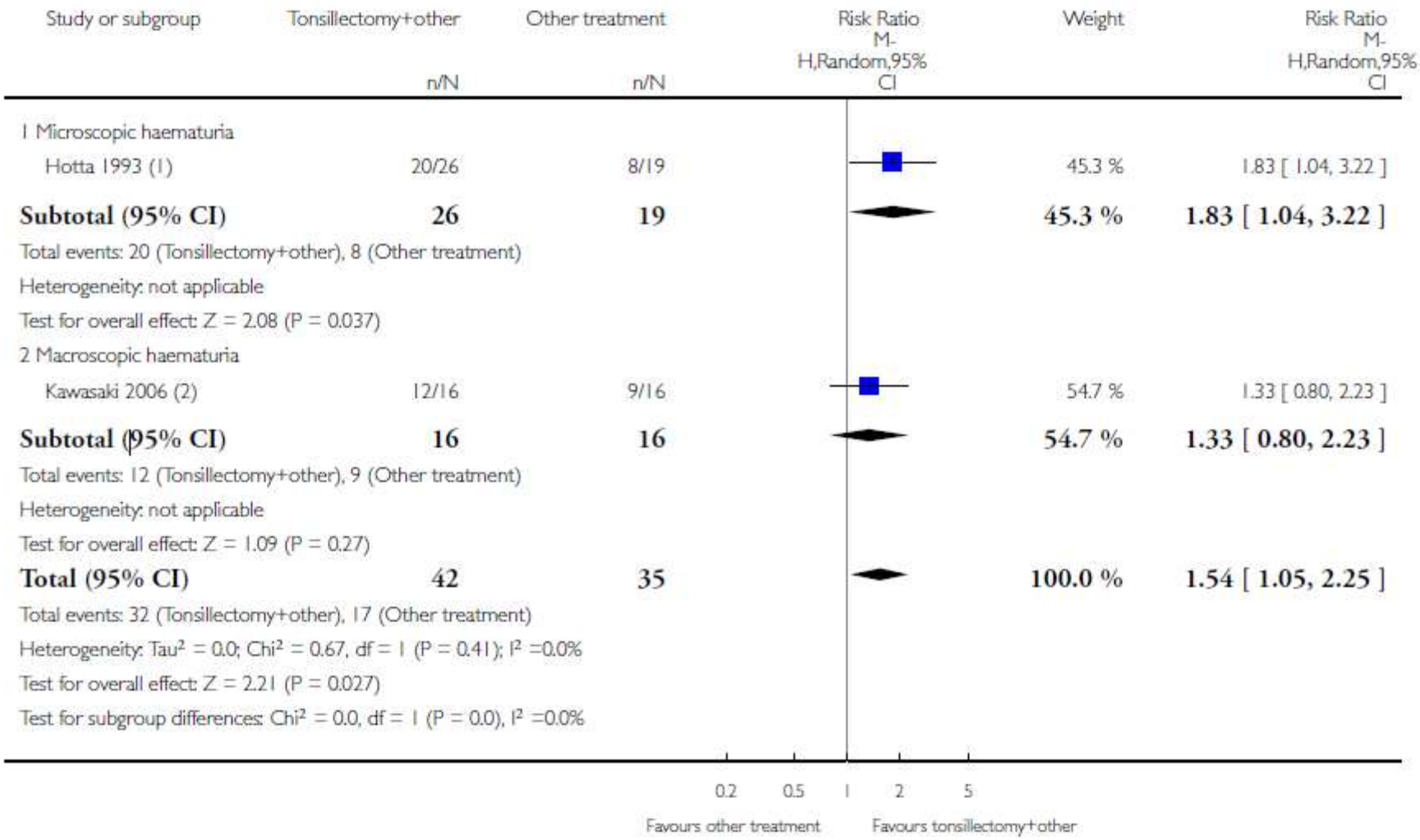
Comparison: 10 Anticoagulant+other treatment versus other treatment

Outcome: 5 Proteinuria

Study or subgroup	Anticoagulant+other N	Mean(SD)[g/24 h]	Other treatment N	Mean(SD)[g/24 h]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Frasca 1997 (1)	10	0.4 (0.2)	10	0.9 (0.6)		-0.50 [-0.89, -0.11]

(1) Anticoagulant+steroid versus steroid

Tonsillectomy



Statins

Analysis 13.2. Comparison 13 Statins+other treatment versus other treatment, Outcome 2 Creatinine clearance.

Review: Non-immunosuppressive treatment for IgA nephropathy

Comparison: 13 Statins+other treatment versus other treatment

Outcome: 2 Creatinine clearance

Study or subgroup	Statins+ other treatment N	Mean(SD)	Other treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Kano 2003 (1)	15	133.1 (14.9)	15	110.5 (15.2)		22.60 [11.83, 33.37]

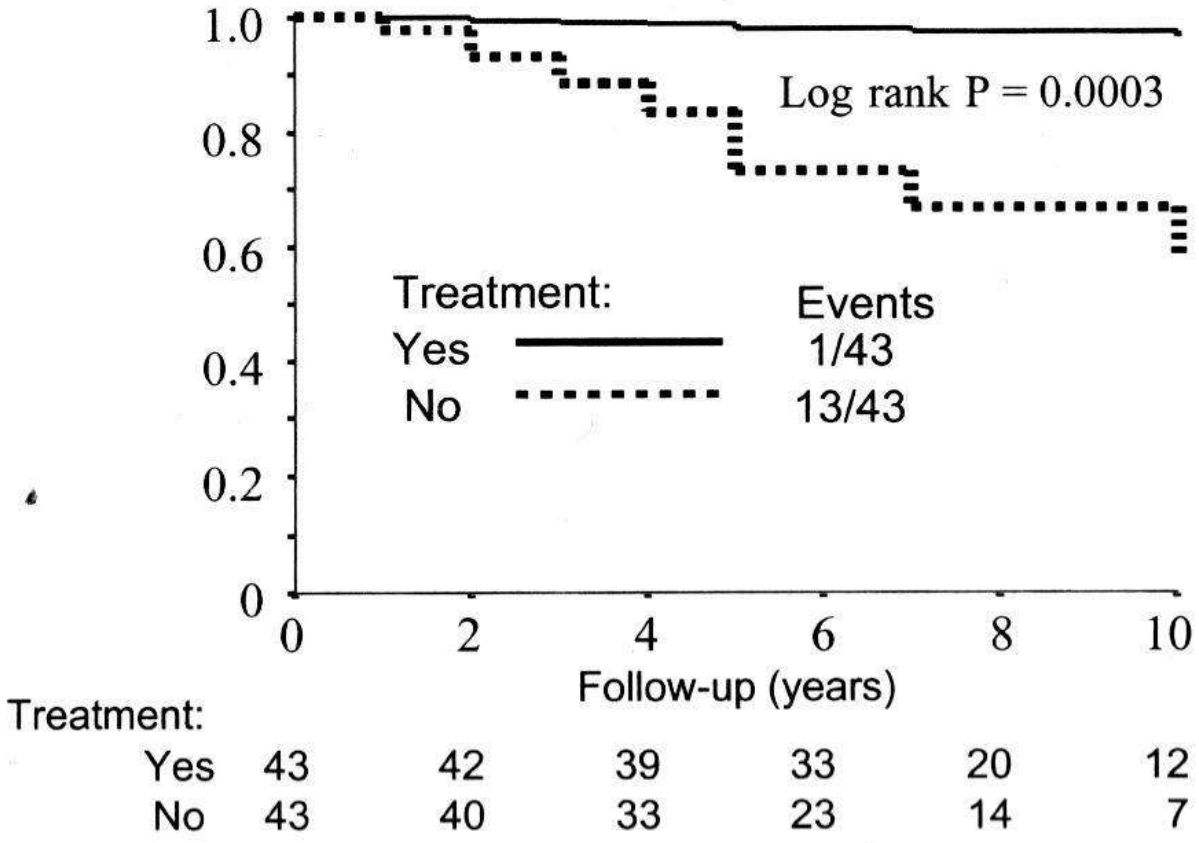
(1) Statin+anticoagulant versus anticoagulant.

Role of immunosuppressive medications

Role of steroid in IgAN

- **We suggest that patients with persistent proteinuria ≥1 g/d, despite 3-6 months of optimized supportive care (including ACEi or ARBs and blood pressure control), and GFR >50 ml/min, receive a 6-month course of corticosteroid therapy (2C)**

Corticosteroid regimens in patients with IgAN

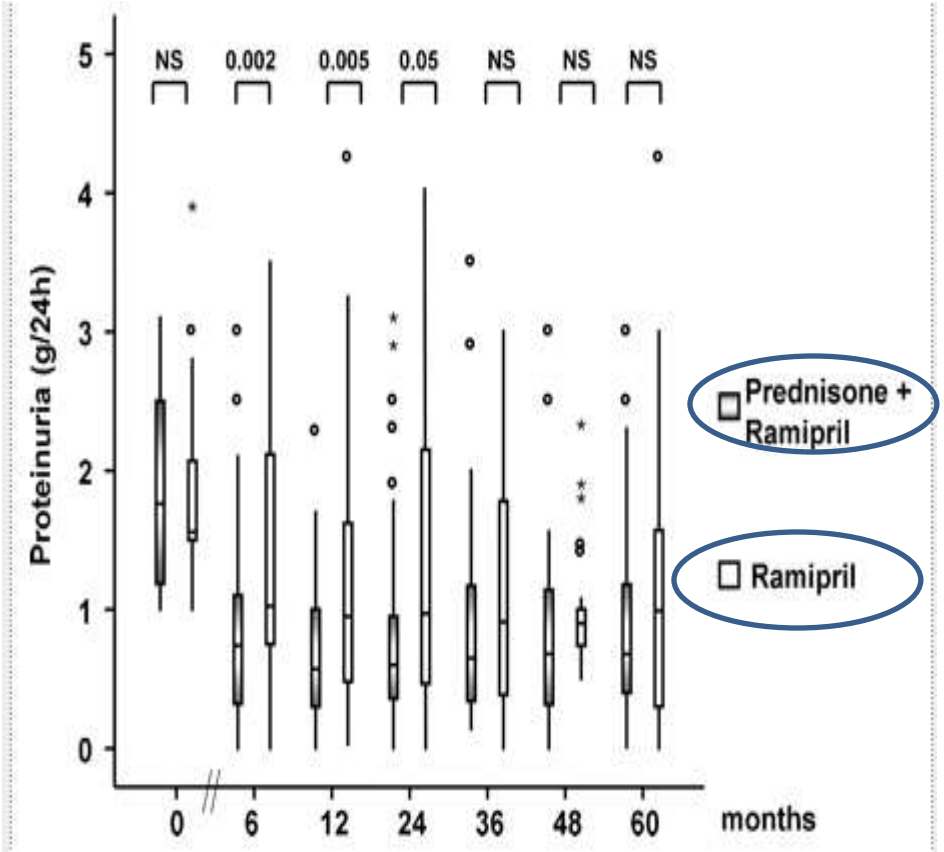


Survival without end point -doubling of serum creatinine

i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months

Pozzi C et al Lancet 1999; 353; 883 -JASN 2004; 15: 157

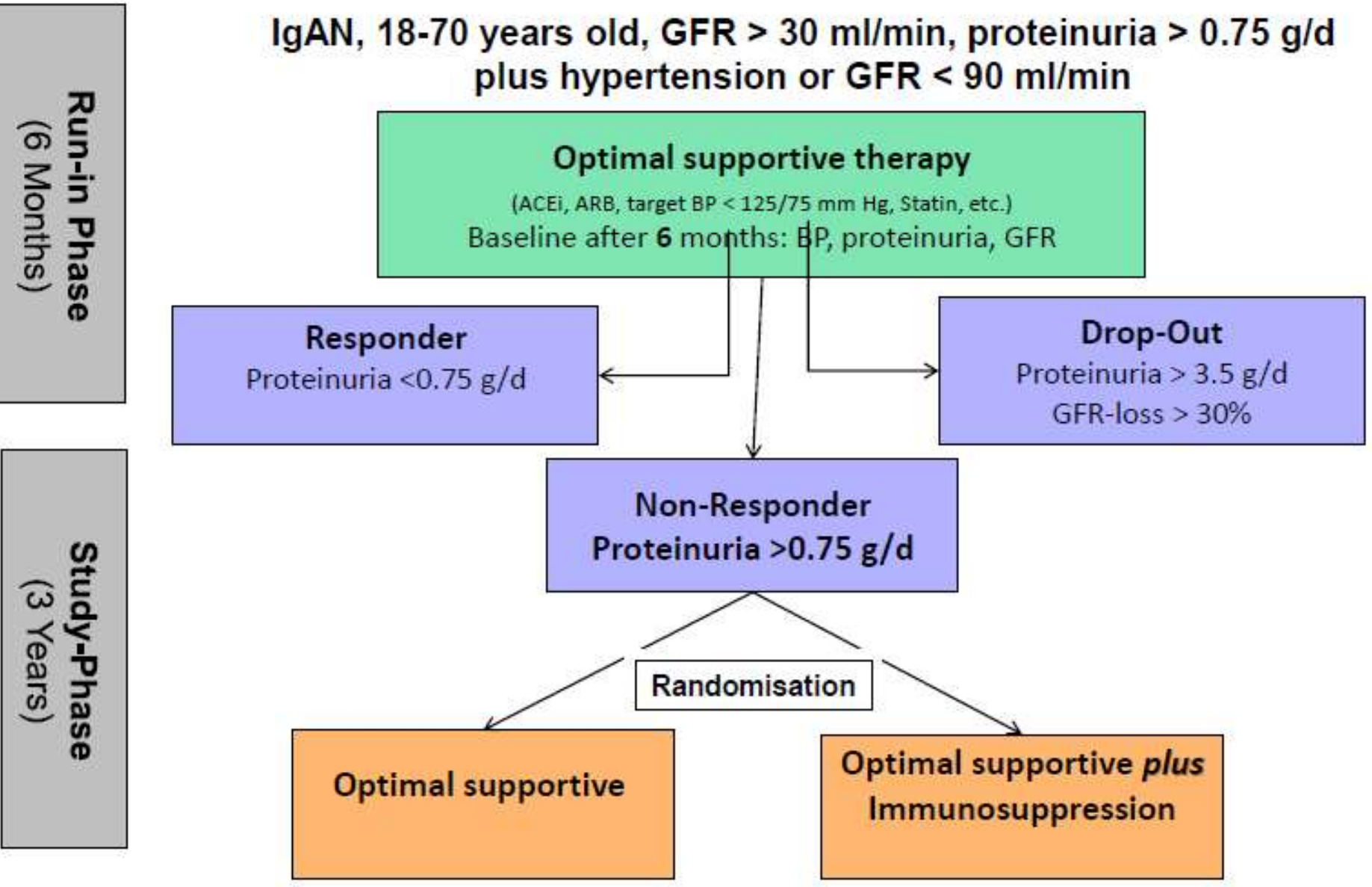
Corticosteroid regimens in patients with IgAN



6-month regimen of oral prednisonea starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

- **Lv J et al.2009 AJKD; 53: 26**
- **Manno C et al. NDT 2009; 24: 3694**

Study Design



STOP IgAN: Results

Two primary end points at 36 months

1. full clinical remission (uPCR <0.2g/g and stable kidney function, or fall in eGFR <5ml.min)
2. eGFR decrease >15ml/min/1.73m^2 from baseline at the end of the trial.

Full clinical remission - uPCR <0.2g/g

4/80 (5%) supportive care - 14/82 (17%) immunosuppression (p=0.01)

BUT

Mean proteinuria at 36 months **not** different (i.e. heterogeneous response)

eGFR at 36 months **not** different

Rauen T et al. NEJM 2015; 373:2225

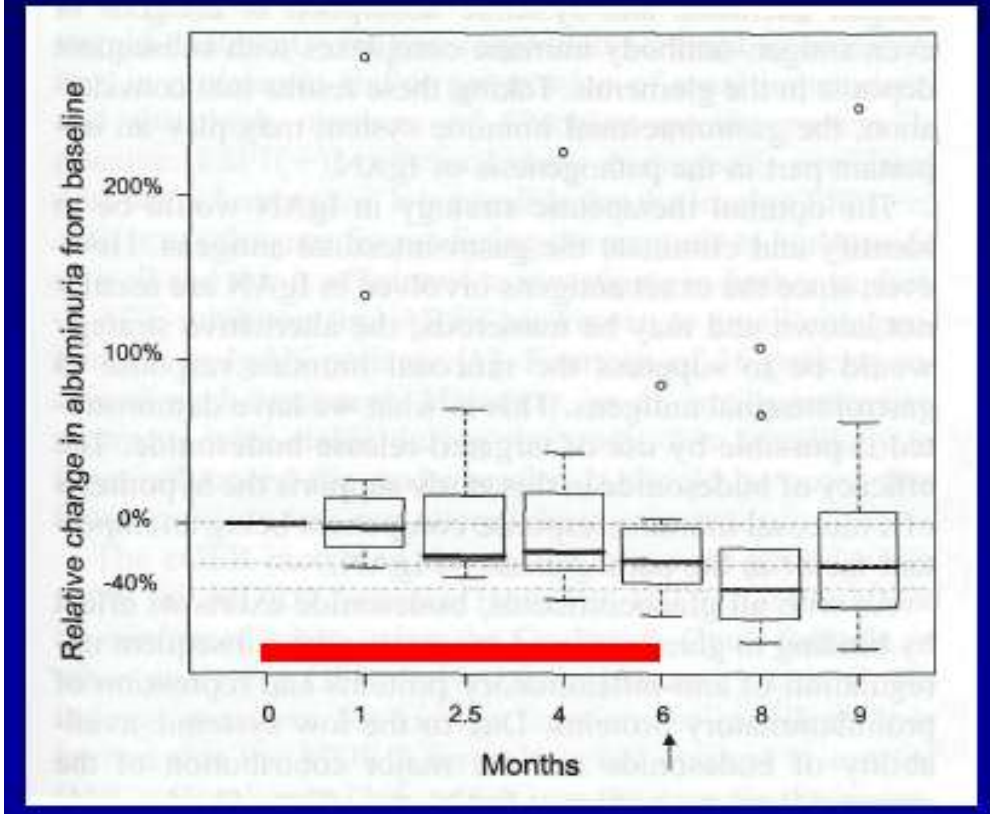
STOP IgAN: Conclusions

- **Remission of proteinuria without protection of eGFR is not a worthwhile goal given adverse effects of immuno-suppressions.**
- **With optimized supportive care .....effects of immunosuppression are markedly blunted in high risk IgAN.**

PILOT STUDY OF ENTERIC BUDESONIDE IN PROTEINURIC IgA NEPHROPATHY

Enteric corticosteroid preparation designed for ileo-caecal release of active compound with limited systemic effect

n = 16 - Ualb > 500mg/d - sCreatinine < 200µmol/l



eGFR (MDRD)

rose by 8% (p=0.003)

Smerud HK *et al.* NDT 2011; 26: 3237

Immunosuppressive agents

- We **suggest** not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney Function).
- We **suggest** not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73m2 unless there is crescentic IgAN with rapidly deteriorating kidney function.
- We **suggest** not using MMF in IgAN. (2C)

Azathioprine

Azathioprine

Supplementary table 55. Summary table of RCTs examining AZA in combination vs. AZA along in biopsy-proven IgA nephropathy (categorical outcomes)

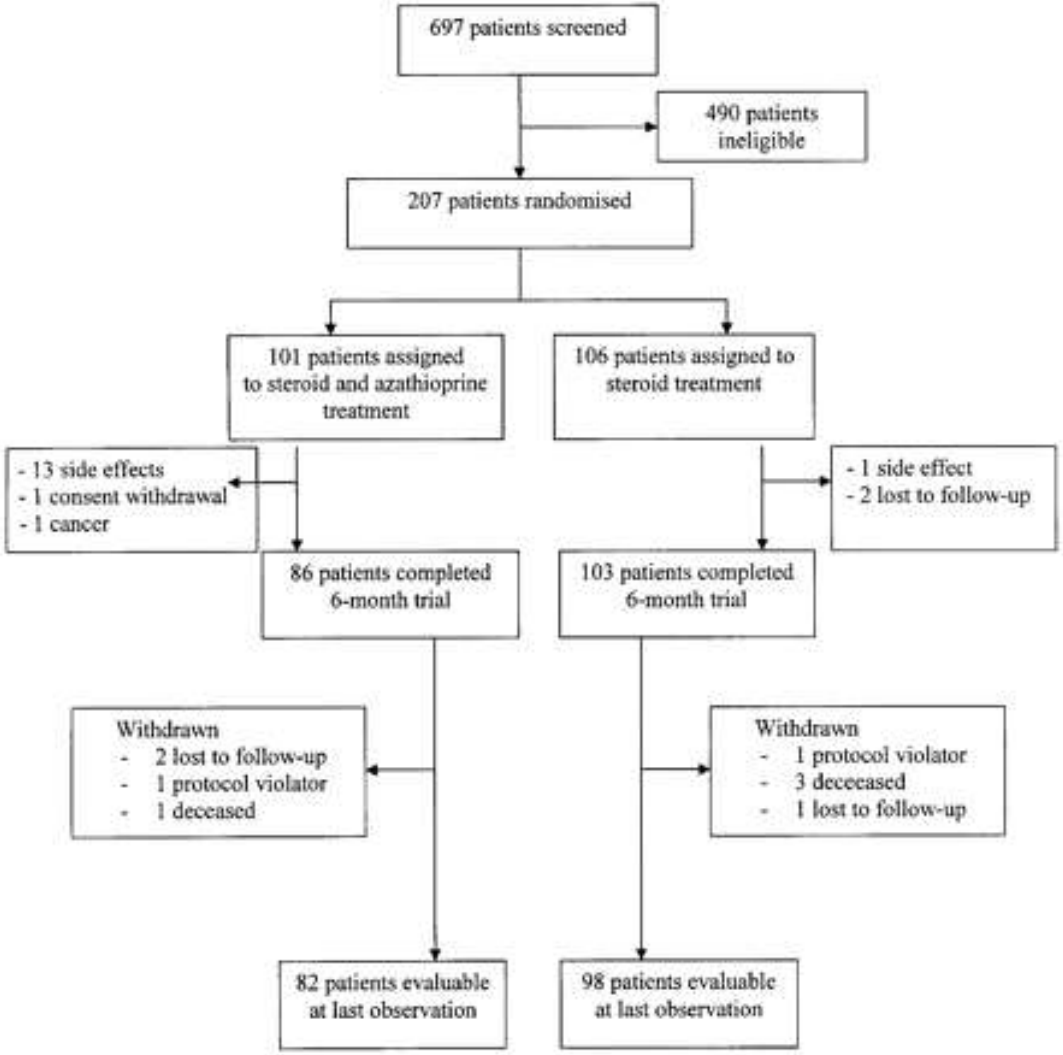
Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
Proteinuria													
Proteinuria disappearance (<0.1 g/m²/d)	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m² Scr 49 µmol/l	1.30 g/m²/d	0%	36 (92%) [29 (74%)]	RR 1.24 (1.01-1.52)[136]	0.039	Good
↓Proteinuria >50% from baseline	Pozzi 2010[67] Italy and Switzerland	5 y (6 mo)	AZA, prednisone alternate day	Prednisone alternate day	101 (101)	106 (106)	GFR 66 ml/min/1.73 m² Scr 106 µmol/l	2.0 g/d	46%	45 (45%) [53 (50%)]	RR 0.89 (0.67-1.19)[137]	NS	Good
S_{Cr}/GFR/CrCl													
CrCl <60 ml/min/1.73m²	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m² Scr 49 µmol/l	1.30 g/m²/d	0%	0% [0%]	--	NS	Good
↑SCr >50% from baseline	Pozzi 2010[67] Italy and Switzerland	5 y (6 mo)	AZA, prednisone alternate day	Prednisone alternate day	101 (101)	106 (106)	GFR 66 ml/min/1.73 m² Scr 106 µmol/l	2.0 g/d	46%	13 (13%) [12 (11%)]	RR 1.14[138] (0.54-2.37)	NS	Good

Azathioprine

Supplementary table 56. Summary table of RCTs examining AZA in combination vs. AZA alone in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
UPE	Yoshikawa 2006[90] Japan	2 y (2 y)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	g/m^2/d	1.29 (1.16)	-1.19 (-1.04)	NS	Good
UPE	Pozzi 2010[67] Italy and Switzerland	5 y (6 mo)	AZA, prednisone alternate day	Prednisone alternate day	101 (101)	106 (106)	GFR 66 ml/min/1.73 m^2 Scr 106 µmol/l	2.0 g/d	46%	g/d	2.10 (1.95)	-0.94 (-0.97)	NS	Good
S_{Cr}/GFR/CrCl														
CrCl	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	39 (40)	39 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	ml/min/ 1.73 m^2	148 (156)	+8 (-1)	NS	Good
Biopsy														
Glomeruli showing sclerosis	Yoshikawa 2006[90] Japan	24 mo (24 mo)	AZA, warfarin, dipyridamole, prednisolone	Prednisolone	32 (40)	30 (40)	GFR 147 ml/min/1.73 m^2 Scr 49 µmol/l	1.30 g/m^2/d	0%	%	5.0 (3.1)	-0.4 (+11.5)	nd	Good
Glomeruli showing crescents											17.3 (19.1)	-15.6 (-18.2)	nd	
Glomeruli showing capsular adhesions											5.2 (3.6)	+0.1 (+1.4)	nd	

Azathioprine



- **Pozzi C et al, *JASN 2010; 21 (10): 1783-90*.**

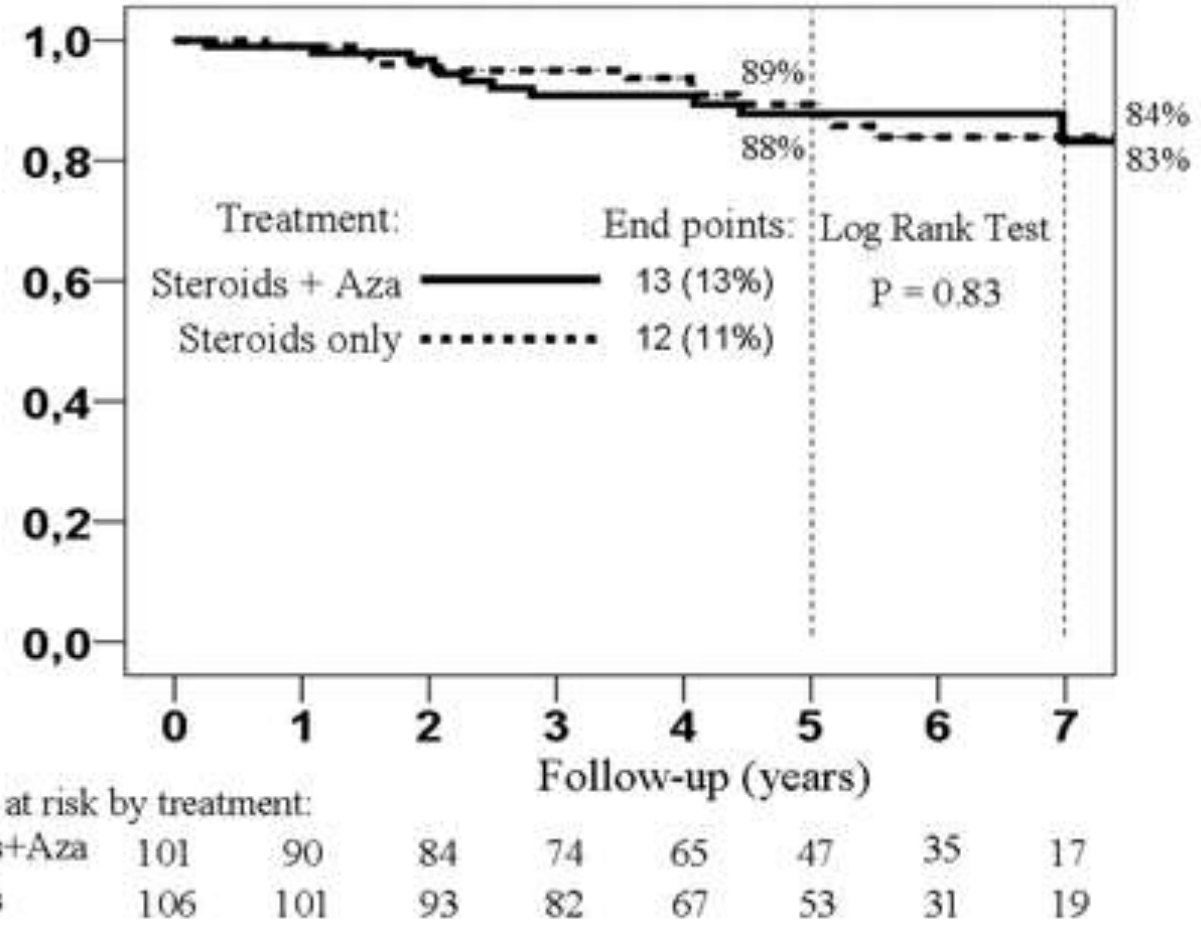
Azathioprine

Baseline clinical and laboratory characteristics by treatment group

	Treatment		Total	*P*
	Group 1 Steroids + Aza	Group 2 Steroids Alone		
No. patients	101	106	207	
Gender (male/female)	76/25 (75/25%)	75/31 (71/29%)	151/56 (73/27%)	0.59
Age (years)	34.8 (27.7 to 43.9)	40.5 (30.3 to 51.3)	36.4 (28.4 to 48.0)	0.02
Body weight (kg)	72.5 (63.3 to 83.0)	74.5 (64.0 to 81.5)	73 (64 to 83)	0.89
Systolic blood pressure (mmHg)	130 (120 to 140)	130 (120 to 140)	130 (120 to 140)	0.86
Diastolic blood pressure (mmHg)	80 (76 to 90)	80 (75 to 90)	80 (75 to 90)	0.40
No. patients treated for hypertension	67 (66%)	74 (70%)	141 (68%)	0.66
No. patients with RAS blockade before starting the study	42 (42%)	53 (50%)	95 (46%)	0.27
no. patients treated with ACEIs	33 (33%)	32 (30%)	65 (31%)	0.77
no. patients treated with ARBs	4 (4%)	7 (7%)	11 (5%)	0.54
no. patients treated with ACEIs and ARBs	5 (5%)	14 (13%)	19 (9%)	0.05
No. patients treated with statins	13 (13%)	13 (12%)	26 (13%)	1.00
Time from biopsy to enrollment (years)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.3)	0.1 (0.0 to 0.3)	0.84
No. patients with macrohematuria at presentation	25 (24.8%)	21 (19.8%)	46 (22.2%)	0.32
Plasma creatinine (mg/dl)	1.20 (1.00 to 1.50)	1.28 (1.00 to 1.66)	1.20 (1.00 to 1.60)	0.20
Estimated creatinine clearance[31]	83 (64 to 113)	80 (58 to 95)	81 (60 to 106)	0.07
GFR estimated using MDRD-4 variables[32]	72 (53 to 88)	63 (44 to 85)	66 (48 to 87)	0.06
Proteinuria (g/d)	2.1 (1.5 to 3.5)	2.0 (1.5 to 2.7)	2.0 (1.5 to 3.0)	0.08

- Median values and interquartile ranges, or numbers and percentages. *P* values of differences between groups: Mann–Whitney test (for continuous variables) or Fisher's exact test (for categorical variables).

Azathioprine



Pozzi C et al, *JASN 2010; 21 (10): 1783-90.*

MMF

Supplementary table 59. Summary table of RCTs examining MMF in biopsy-proven IgA nephropathy (categorical outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
ESRD													
ESRD	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d + ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m²	2.7 g/24hr	Total 100%	5 (29%) [2 (13%)]	Adjusted HR 1.74 0.07–42.3	NS	Fair
Cumulative % free of death or ESRD	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m²	1.9 g/d	Total 100%[139]	89% [92%]	--	NS	Fair
ESRD	Tang 2005, 2010[79;80] Hong Kong	6 y (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m²	1.8 g/d	Total 100%	2 (10%) [9 (45%)]	RR 0.22 (0.05- 0.90)[140]	0.015	Fair
Doubling of S_{Cr} or ESRD		18 mo (6 mo)								1 (5%) [3 (15%)]	RR 0.33 (0.04-2.94)	NS (0.323)	Fair
		6 y (6 mo)								3 (15%) [10 (50%)]	RR 0.30 (0.10-0.93)	0.037	Fair
Kidney Function													
↑S_{Cr} 50%	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d + ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m²	2.7 g/24hr	Total 100%	5 (29%) [2 (13%)]	Adjusted HR 1.62 (0.07–35.6)	NS	Fair
↑S_{Cr} 0.5 mg/dl										10 (59%) [7 (47%)]	Adjusted HR 2.84 (0.6–14.6)	NS	
↓Inulin clearance ≥ 25%	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m²	1.9 g/d	Total 100%[141]	33% [15%]	nd	NS	Fair
↑S_{Cr} ≥ 50%										14% [0 (0%)]	nd	NS	
Proteinuria													

MMF

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results		*P* value	Quality
			Intervention	Control	Intervention	Control				Events (%) Intervention [Control]	RR/OR/HR		
↓24 h protein excretion 50%	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d+ ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m²	2.7 g/24hr	Total 100%	3 (18%) [2 (13%)]	RR 1.32 (0.25-6.88)[142]	NS (0.739)	Fair
Remission of proteinuria	Tang 2005[79] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m²	1.8 g/d	Total 100%	16 (80%) [6 (30%)]	RR 2.67 (1.32-5.39)[143]	0.006	Fair
Adverse Event													
Treatment discontinuation	Frisch 2005[28] US	2 y (1 y)	MMF 1000 mg 2x/d+ ACE-I	Placebo 1000 mg 2x/d + ACE-I	17 (17)	15 (15)	GFR 38 ml/min/1.73m²	2.7 g/24hr	Total 100%	2 (11%) [2 (13%)]	RR 0.88 (0.14-5.52)[144]	NS (0.894)	Fair
MMF dose adjustment due to AE	Tang 2005[79] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m²	1.8 g/d	Total 100%	Anemia (n=3) Diarrhea (n=1) Infection (n=3)	--	nd	Fair
Adverse event	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m²	1.9 g/d	Total 100%[145]	Discontinuation of MMF due to TB (n=1) Dose reduction due to anemia (n=2) Transient leucopenia (n=1) [Placebo pregnancy uneventful n=1 Rectal carcinoma n=1)	--	nd	Fair

MMF

Supplementary table 60. Summary table of RCTs examining MMF in biopsy-proven IgA nephropathy (continuous outcomes)

Outcome	Study, Year Country	Duration Outcome measurement (Treatment)	Description		No. Analyzed (Enrolled)		GFR/S_{Cr}	Proteinuria	ACE-I or ARB use	Results			*P* value	Quality
			Intervention	Control	Intervention	Control				Units	Baseline Intervention (Control)	Δ Intervention (Control)		
Proteinuria														
Mean urine protein loss	Tang 2005 2010[79;80] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m²	1.8 g/d	Total 100%	g/d	1.8 (1.87)	-0.66 (+0.53)	0.009	Fair
		2y - 6 y (6 mo)									1.8 (1.87)	nd	NS	Poor
ΔProteinuria	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I(aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m²	1.9 g/d	Total 100% [146]	g/d	1.9 1.3	-0.3 (-0.3)	NS	Fair
S_{Cr}/GFR/CrCl														
Annualized median ΔS_{Cr}	Maes 2004[52] Belgium	3 y (3 y)	MMF 2 g/d, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	Placebo lactose cap, (<5 g NaCl/d), ACE-I (aimed BP 125/75 mmHg)	21 (21)	13 (13)	GFR 73 ml/min/1.73 m²	1.9 g/d	Total 100% [147]	mg/dl/y	1.46 (1.39)	+0.11 (+0.05)	NS	Fair
ΔInulin clearance										ml/min/1.73 m²	73 (69)	-13 (-2)	NS	
Annual rates of ΔS_{Cr}	Tang 2005 2009[79;80] Hong Kong	18 mo (6 mo)	MMF 2 g/d ACE-I or ARB for target BP <125/85 mmHg	ACE-I or ARB for target BP <125/85 mmHg	20 (20)	20 (20)	GFR 75 ml/min/1.73 m²	1.8 g/d	Total 100%	mg/dl/yr	1.53 (1.65)	-0.013 (+0.108)	NS	Good
Annual rates of ΔCrCl		18 mo (6 mo)								ml/min/1.73 m²	75 (69)	-3.76 (-1.0)	NS	
		6 y (6 mo)										-1.125 (-3.812)	0.021	

Ongoing trials

9 studies found for: "IgA nephropathy" AND "MMF"

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Rank	Status	Study
1	Completed	An Multi-site Prospective Study to Assess the Efficacy and Safety of MMF in the Treatment of Proliferative IgA Nephropathy(IgAN) **Condition:** IgA Nephropathy (IgAN) **Interventions:** Drug: mycophenolate mofetil plus lower dose of Prednisone; Drug: Prednisone in full dose
2	Recruiting	Mycophenolate Mofetil (MMF) in Patients With IgA Nephropathy (IgAN) **Condition:** IgA Nephropathy **Interventions:** Drug: irbesartan; Drug: methylprednisolone (MP) or prednisone (pred); Drug: mycophenolate mofetil (MMF)
3	Terminated Has Results	Mycophenolate Mofetil (MMF) in Patients With IgA Nephropathy **Condition:** IgA Nephropathy **Interventions:** Drug: Mycophenolate Mofetil (MMF); Drug: MMF Placebo; Drug: ACEi; Drug: FOS
4	Completed	Mycophenolate Mofetil Versus Intravenous Cyclophosphamide Pulses in the Treatment of Crescentic IgA Nephropathy **Condition:** IGA Nephropathy

Mycophenolate Mofetil (MMF) in Patients With IgA Nephropathy

This study has been terminated.

(DSMB recommended stopping the trial because of lack of effect.)

Sponsor:
St. Joseph's Hospital and Medical Center, Phoenix

Information provided by (Responsible Party):
St. Joseph's Hospital and Medical Center, Phoenix

ClinicalTrials.gov Identifier:
NCT00318474

First received: April 24, 2006
Last updated: February 4, 2016
Last verified: February 2016
History of Changes

Purpose

IgA nephropathy (IgAN) is the most common type of glomerulonephritis worldwide. 15-40% of individuals diagnosed with IgAN, including children, will eventually progress to chronic renal insufficiency (CRI) and end stage renal disease (ESRD). The study is to evaluate the safety and benefits of **MMF** in patients with IgAN who have been pre-treated (and continue to be treated) with angiotensin converting enzyme inhibitors (ACEi) and fish oil supplements (FOS).

Condition	Intervention	Phase
IgA Nephropathy	Drug: **Mycophenolate** Mofetil (**MMF**) Drug: **MMF** Placebo Drug: ACEi Drug: FOS	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)

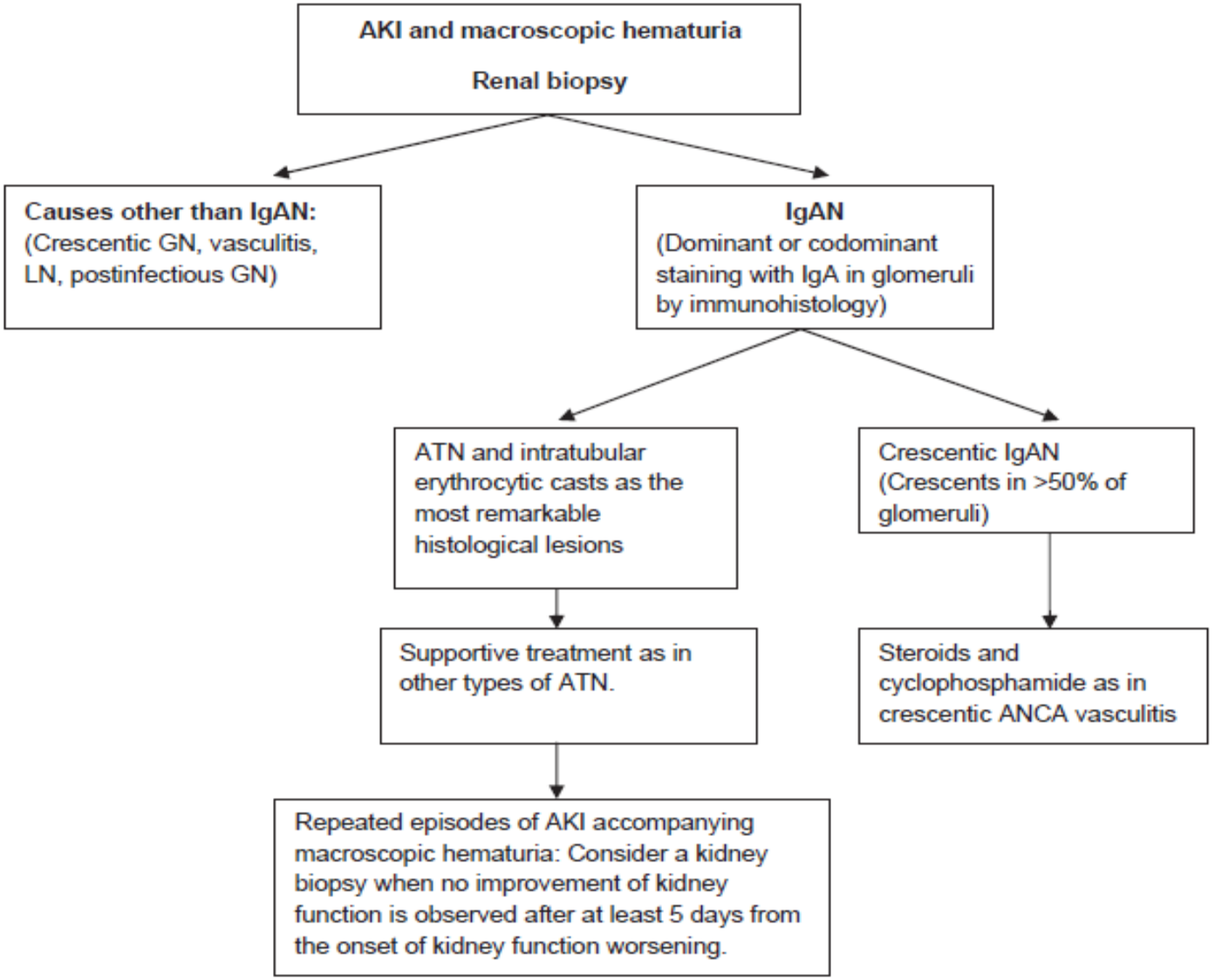
Atypical forms of IgAN

- AKI associated with macroscopic hematuria.
- Crescentic IgAN.
- MCD with mesangial IgA deposits leading to nephrotic range proteinuria with microscpic hematuria.

AKI associated with macroscopic hematuria

- **We suggest general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing only ATN and intratubular erythrocyte casts.**
- **Perform a repeat kidney biopsy in IgAN patients with AKI associated with macroscopic hematuria if there is no improvement after 5 days from the onset of kidney function worsening.**

Management algorithm of patients with AKI associated with macroscopic hematuria.



Crescentic IgAN

- Crescentic IgAN is defined as IgAN with crescents in **>50% of glomeruli** with **rapidly progressive renal deterioration.**
- We **suggest** the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis

Recommended treatment regimens for ANCA vasculitis with GN

Agent	Route	Initial dose
Cyclophosphamide[a]	i.v.	0.75 g/m^2 q 3-4 weeks. Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3.
Cyclophosphamide[b]	p.o.	1.5–2 mg/kg/d, reduce if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust the daily dose to keep leucocyte count >3000/mm^3.
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3–4 months.
Rituximab[c]	i.v.	375 mg/m^2 weekly × 4.
Plasmapheresis[d]		60 ml/kg volume replacement. *Vasculitis*: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. *Vasculitis in association with anti-GBM antibodies*: Daily for 14 days or until anti-GBM antibodies are undetectable.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; i.v., intravenous; p.o., orally.

[a]Given with pulse and oral steroids. An alternative i.v. cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.[705]

[b]Given with pulse and oral steroids.

[c]Given with pulse and oral steroids.

[d]Not given with pulse methylprednisolone. Replacement fluid is 5% albumin. Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.

Nephrol Dial Transplant (2003) 18: 1321–1329
DOI: 10.1093/ndt/gfg081

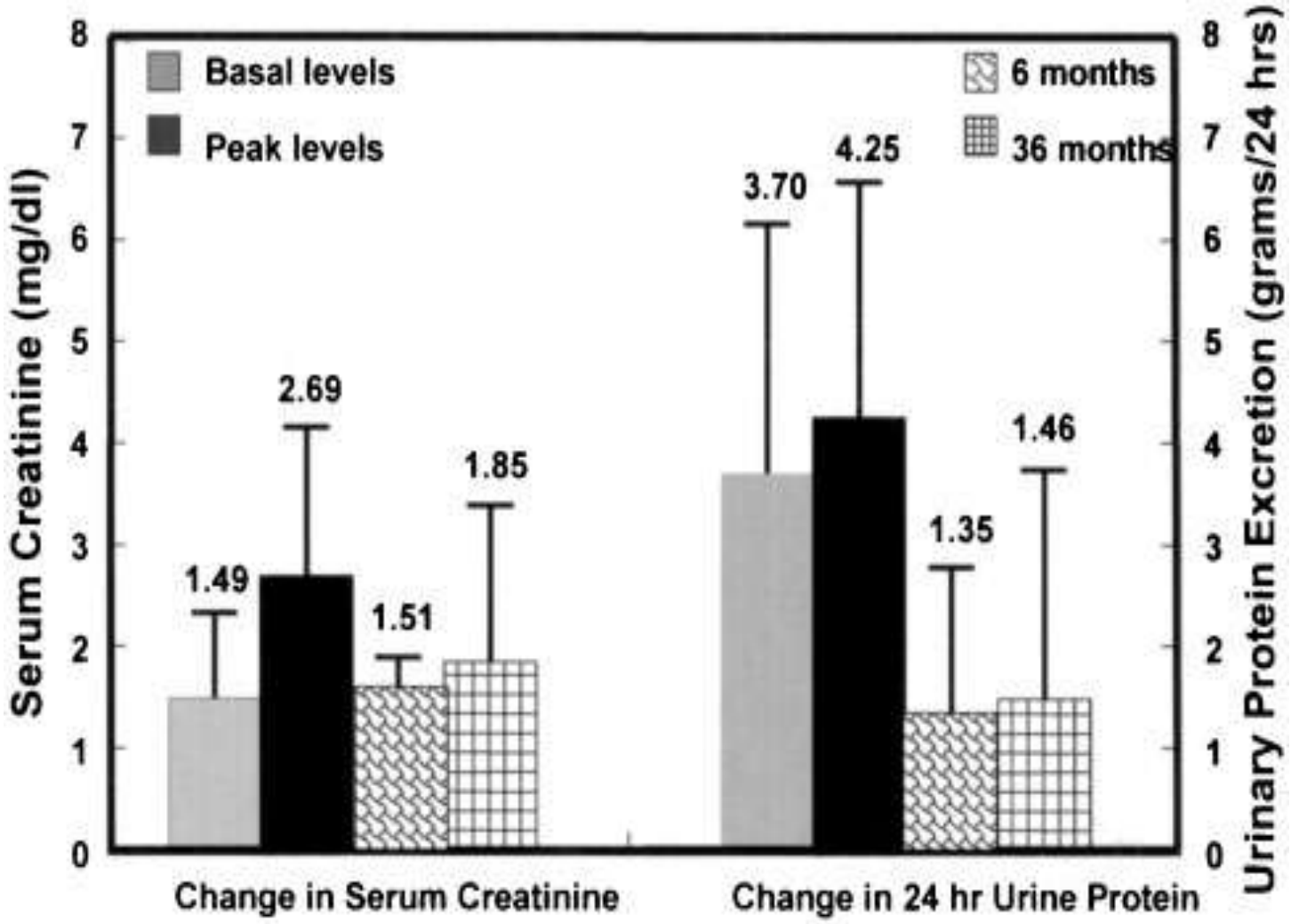
Nephrology
Dialysis
Transplantation

Original Article

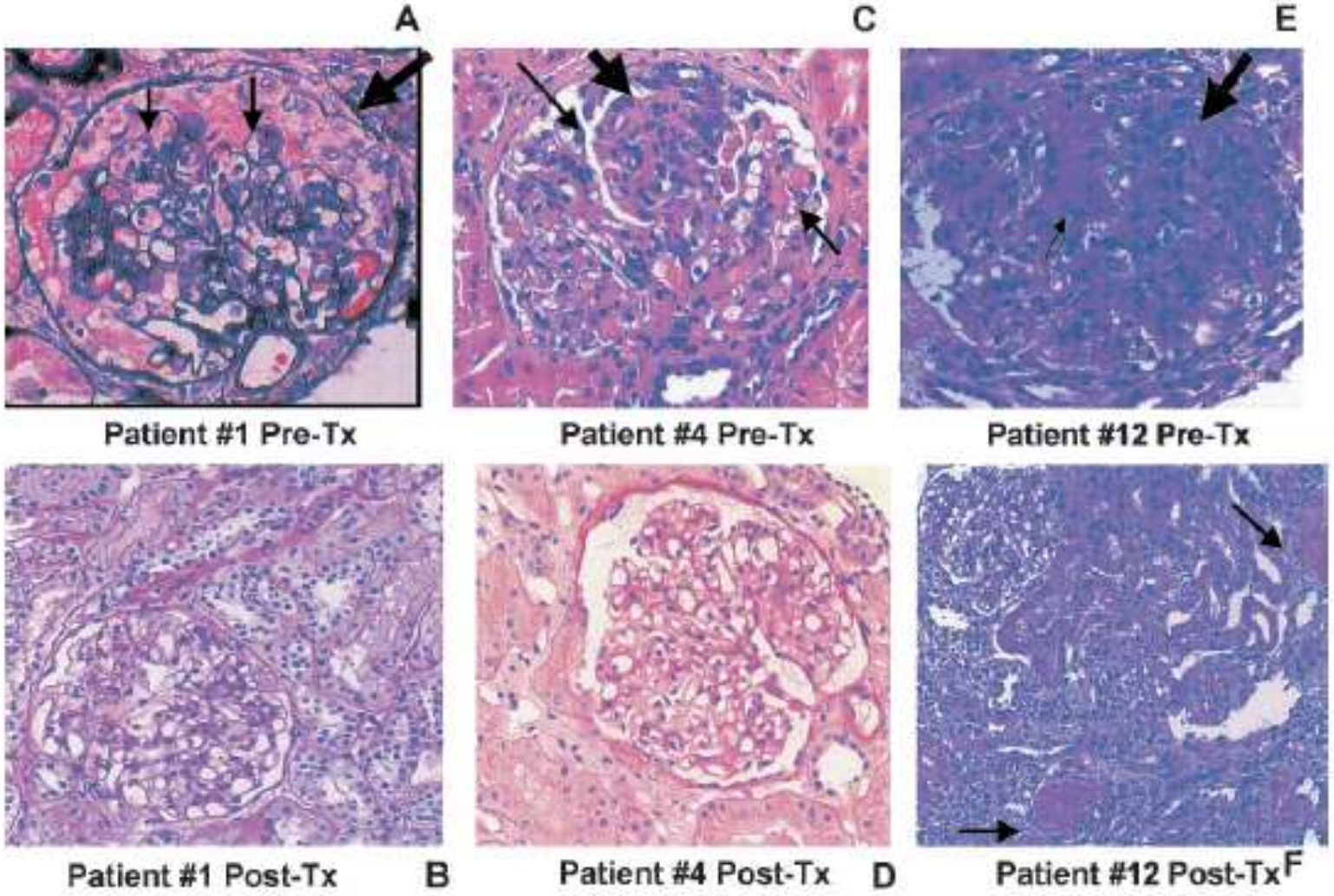
Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide

James A. Tumlin[1], Verachai Lohavichan[1] and Randy Hennigar[2]

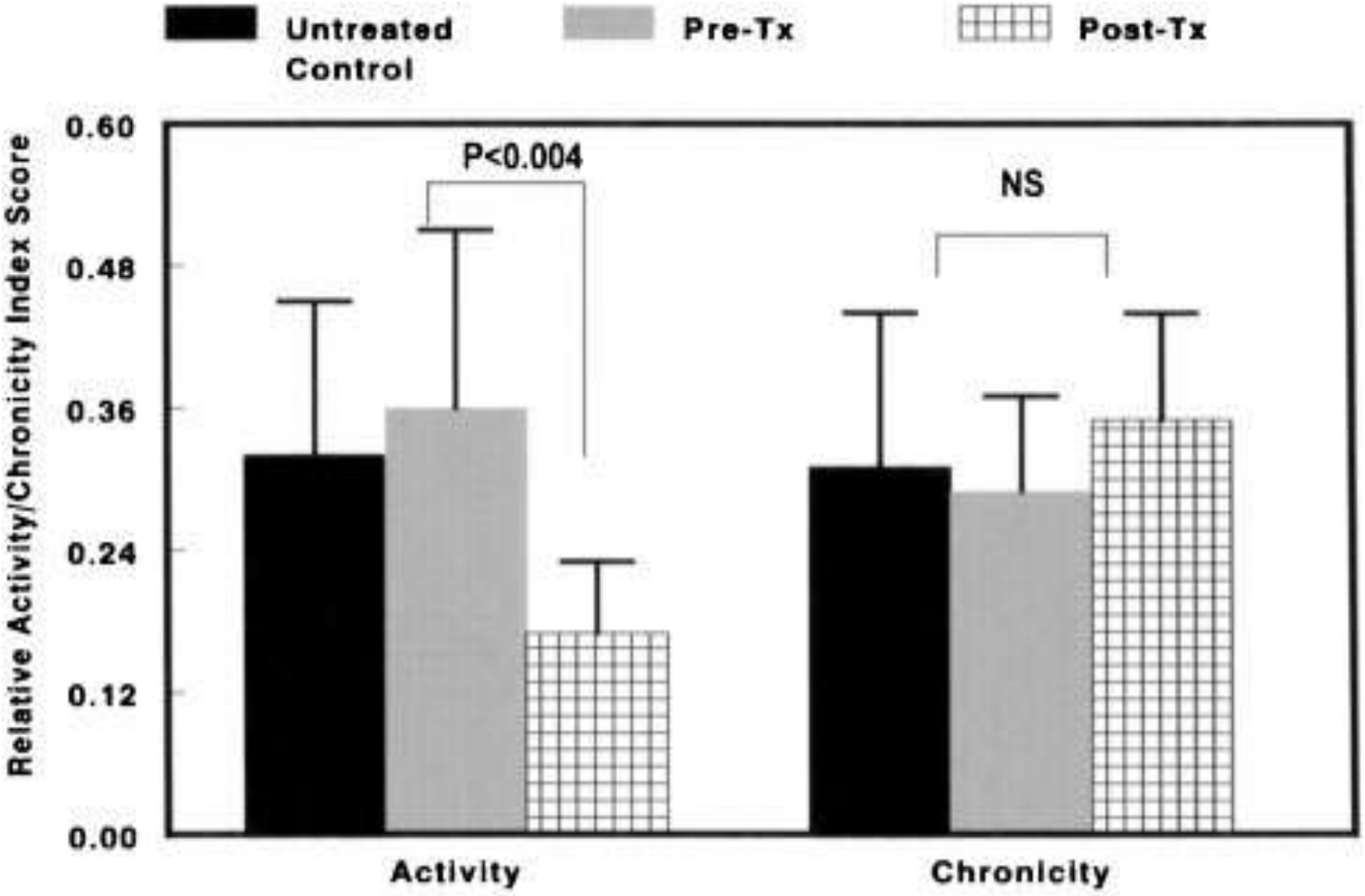
[1]Division of Nephrology and [2]Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA



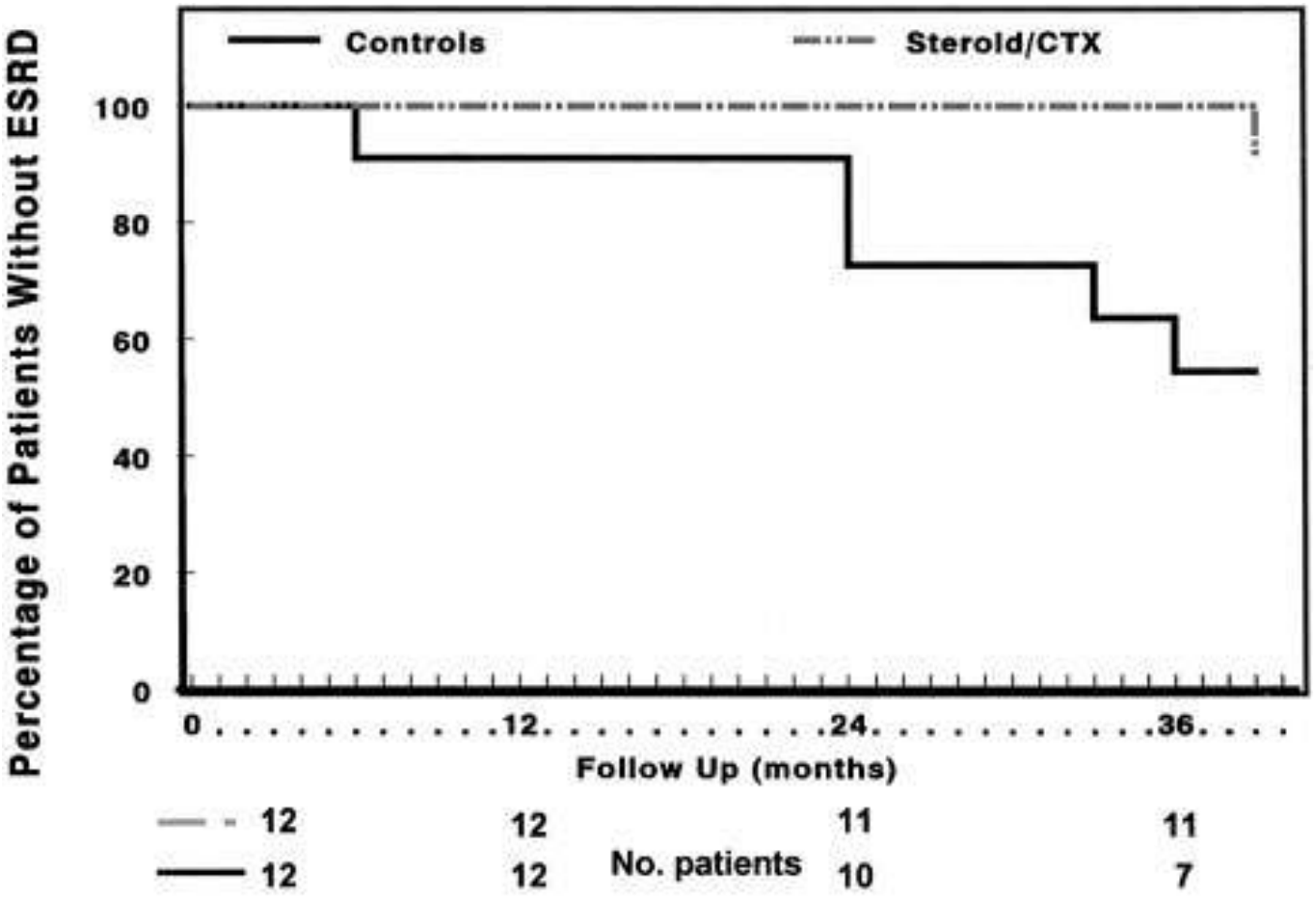
Tumlin J et al. Nephrol Dial Transplant 2003; 18: 1321–29



Tumlin J et al. Nephrol Dial Transplant 2003; 18: 1321–29



Tumlin J et al. Nephrol Dial Transplant 2003; 18: 1321–29



Tumlin J et al. Nephrol Dial Transplant 2003; 18: 1321–29

New therapeutic options in crescentic IgAN

CLINICAL KIDNEY JOURNAL

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Leading European Nephrology

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doi: 10.1093/ckj/sfv076
Advance Access Publication Date: 27 August 2015
Exceptional Case

EXCEPTIONAL CASE

Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum?

Troels Ring[1], Birgitte Bang Pedersen[1], Giedrius Salkus[2], and Timothy H.J. Goodship[3]

[1]Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark, [2]Department of Pathology, Aalborg University Hospital, Aalborg, Denmark, and [3]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

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MCD with mesangial IgA deposits

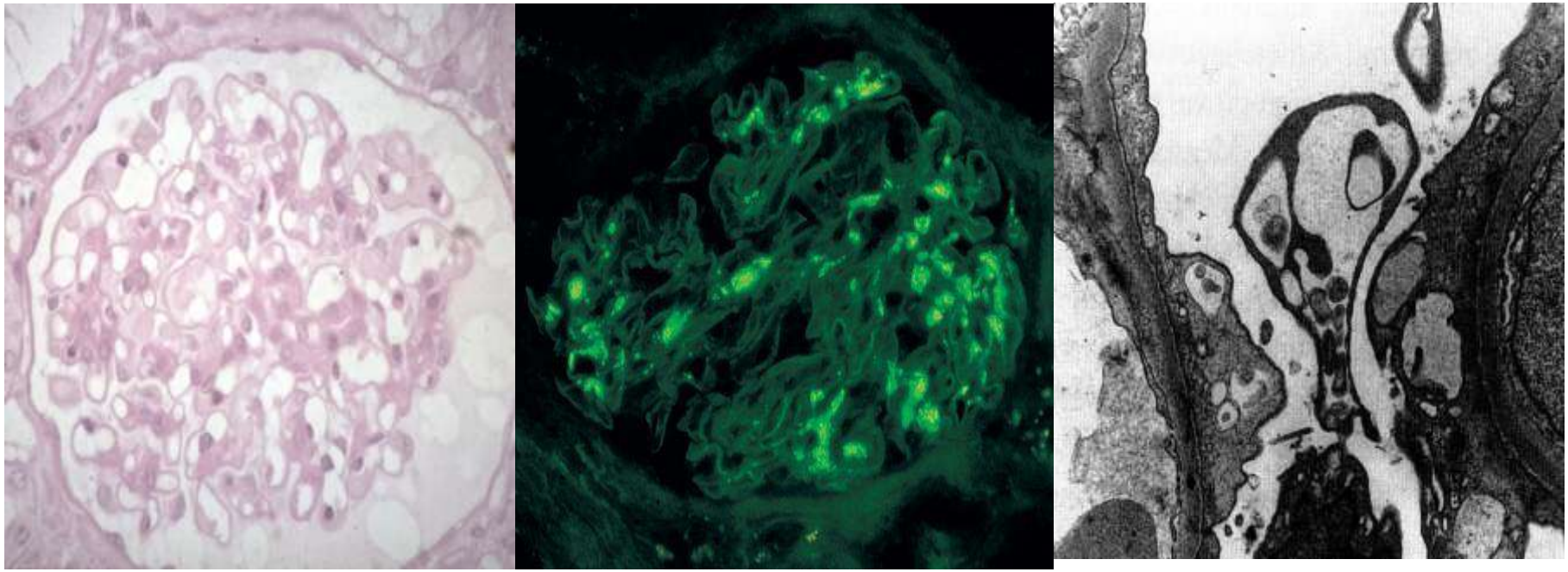
- **We recommend treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. (1B)**

MCD with mesangial IgA deposits

- **IgAN and nephrotic range proteinuria**
- **N = 233**
- **Much more likely to have normoalbuminaemia than minimal change**

Chen M et al. NDT 2011; 26: 1247

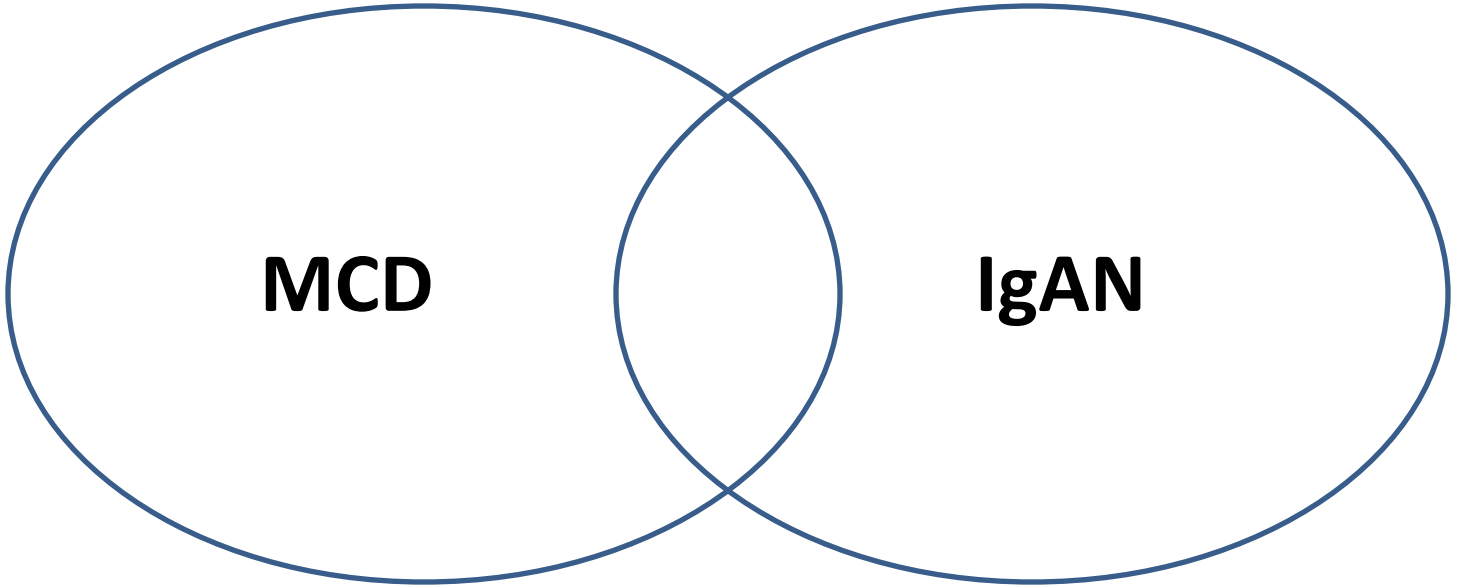
MCD with mesangial IgA deposits



- **Corticosteroids: complete remission of nephrotic syndrome**
- **Microscopic haematuria persists**

MCD with mesangial IgA deposits

- **Two common glomerular diseases coincide……**



Chen M et al. NDT 2011; 26: 1247

MCD with mesangial IgA deposits

- **Single centre cohort study: n = 27**
- **Age 18-60 yrs**
- **Prednisone 1mg/kg until complete remission , then taper**

COMPLETE REMISSION RATE

Weeks	1	2	4	8
%	4	48	93	100

Subsequent relapses –2 patients only

Wang J *et a*l. NDT 2013 Sep;28(9):2339-45

Risk assessment for IgAN then treat accordingly

Features of a poor prognosis at presentation

- Heavy proteinuria (>3.5 g/day).
- Hypertension (difficult to control).
- Significant tubulointerstitial fibrosis and glomerulosclerosis on renal biopsy.
- Rapidly progressive crescentic IgAN.
- Impaired renal function.

Risk assessment for IgAN

- *Low-risk patients.*
- *Medium-risk patients.*
- *High-risk patients.*

Low risk	Medium risk	High risk
Normotensive	Hypertension	Hypertension
Proteinuria <500mg/day	Proteinuria >500mg/day	• Significant proteinuria >1g/day • Proteinuria fails to decrease with RAAS-Blockade
Normal GFR	Normal GFR or only slight decrease.	Significantly impaired renal function at outset or progressive decline in GFR.
Isolated microscopic, or episodic macroscopic, haematuria.	Older age.	Difficult to treat, with progression to ESRD not uncommon
		• Crescentic change on biopsy. • Significant chronic histological damage.

Risk assessment for IgAN

- **Low-risk patients: No treatment with** regular surveillance (annual BP, SCr, eGFR, uPCR) is recommended.
- **Medium-risk patients:** Non-immuno-suppressive treatment (dual RAS blockade, Fish oil)
- **High-risk patients:** Non-immuno-suppressive treatment and immuno-suppressive treatment.

Thank you